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APPLICATION NUMBER: 20-547/S007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA 20-547
Supplement No. 007
Zafirlukast 10 mg Tablets
ACCOLATE[R]

Zeneca Pharmaceuticals
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Submission Dates: 9/17/98
2/11/99
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9/10/99

Reviewer: John Hunt

Type of Submission: Pediatric Efficacy Supplement

Synopsis:

Zafirlukast is classified as an oral anti-inflammatory drug that is a selective and competitive receptor antagonist of leukotriene D_4 and E_4 components of slow-reacting substance of anaphylaxis (SRSA). Cysteinyl leukotriene production and receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle constriction, and altered cellular activity associated with the inflammatory process, all of which contribute to the signs and symptoms of asthma.

Zafirlukast (ACCOLATE) was originally approved by FDA on 9/26/96 for, "the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older". Only a 20 mg tablet was approved and the following is stated in the package insert's DOSAGE and ADMINISTRATION section.

> "The recommended dose of ACCOLATE is 20 mg twice daily in adults and children 12 years and older.
>
> Since food reduces the bioavailability of zafirlukast, ACCOLATE should be taken at least 1 hour before or 2 hours after meals.
>
> **Elderly Patients:** Based on cross-study comparisons, the clearance of zafirlukast is reduced in elderly patients (65 years of age and older), such that Cmax and AUC are approximately twice those of younger adults. In clinical trials, a dose of 20 mg twice daily was not associated with an increase in the overall incidence of adverse events or withdrawals because of adverse events in elderly patients.
>
> **Patients with Hepatic Impairment:** The clearance of zafirlukast is reduced in patients with stable alcoholic cirrhosis such that the Cmax and AUC are approximately 50-60% greater than those of normal adults. ACCOLATE has not been evaluated in patients with hepatitis or in long-term studies of patients with cirrhosis.
>
> **Patients with Renal Impairment:** Dosage adjustment is not required for patients with renal impairment."

Via this supplemental NDA (sNDA), Zeneca Pharmaceuticals wishes to get ACCOLATE approved for treating pediatric patients [ ] to 11 years of age. Also, they want to get approval for [ ] new tablet strengths (i.e., [ ] and 10 mg) for this age group. The following is proposed for addition to the DOSAGE and ADMINISTRATION section of the package insert.

[ ]

Included in the sNDA's Human Pharmacokinetics (PK) and Bioavailability (BA) Section were assay validation data, in vitro dissolution data and study reports for the following three in vivo studies.

1. Study No. 9188IL/0144: A fasting single dose crossover bioequivalence (BE) study in 36 healthy adult male subjects where 2 X 10 mg to-be-marketed tablet (MT) was compared to 2 X 10 mg pediatric clinical trial tablet (PCT).

2. Study No. 9188IL/0145: A fasting single dose (2 X 10 mg MT) and multiple dose (2 X 10 mg MT b.i.d.) trial to determine PK, safety, and tolerability in 20 healthy or mildly asthmatic pediatric subjects (9 males/11 females; age 7 to 11 years).

3. Study No. 9188IL/0152: A fasting crossover multiple dose BE study in 26 healthy adult male subjects where 1 X 10 mg PCT b.i.d. was compared to 2 X 5 mg PCT b.i.d.

Also cross-referenced in this sNDA is Study No. 9188IL/0058 that was previously reviewed by OCPB (i.e., review dated 6/20/96) for the original NDA. This was a 2-period, single dose trial in pediatric asthmatics (9 males/9 females; ages 7 to 11 years) where doses of 2, 4, 6-8, 20-25, 30-40 and 50-70 mg were studied using 2, 5, 10, 20 or 40 mg tablet strengths. Each subject received two drug doses (i.e., a low dose and a high dose). [Note: The tested 20-mg tablet had the same formulation as 20 mg MT except for minor coating differences; the other tablet strengths had the same inactive ingredients but they were not proportional to the 20 mg tablet. All tablets had similar dissolution characteristics using a dissolution method that was a modification of the NDA approved dissolution method.]

For the review of this sNDA, the following biopharmaceutic and clinical pharmacology questions are felt to be most critical and relevant as related to the approval requests being made in this application, and as related to meeting the Agency's Bioavailability and Bioequivalence Requirements (21CFR 320).

1. Can the new [ ] and 10 mg tablet strengths be approved?

Answer: Based on i) the new [ ] and 10 mg tablets being compositionally proportional to each other and to the marketed 20 mg tablet, ii) acceptable comparative in vitro dissolution profile data and, iii) acceptable in vivo bioequivalence data (i.e., 10 mg market tablet vs.10 mg pediatric clinical trial tablet,

etc.), the new and 10 mg tablet strengths can be recommended for approval (See review pages 9 to 11 for information/data). However, due to PK/efficacy concerns that are raised in the Answer to Question No. 5 below, it may not be appropriate to approve the tablet at this time if the dosing regimen is not recommended for approval. [It is noted that based upon the newly proposed dosing regimens, children to 11 years would not be expected to receive the 20 mg market tablet.]

2. **Are there any established relationships between systemic zafirlukast plasma levels and pharmacodynamic (PD) related efficacy and/or safety bio-markers, surrogate endpoints or clinical endpoints?**

Answer: From the review of the original NDA, no dose-ordering or PK/PD relationships were established in terms of efficacy related surrogate or clinical endpoints. From this sNDA's pediatric clinical trials (i.e., Study Nos. 9188IL/0075, 9188IL/0079 and 9188IL/0139; see Background section on page 8 for study descriptions), no efficacy related PK/PD relationship could be made or was further attempted as noted as follows.

For Study No. 9188IL/0075 (i.e., where only a single drug plasma concentration was obtained about 4.5 hrs following 5, 10, 20 or 40 mg zarfirlukast single doses), Zeneca states in a 8/26/99 submission that, "No significant association between plasma concentrations and effect were found." For pivotal Study Nos. 9188IL/0079 and 9188IL/0139, sparse drug concentrations were determined but Zeneca did not conduct population PK data analyses because they did not have confidence in the reported drug plasma levels (i.e., problems knowing when plasma samples were taken in relation to doses). Further Zeneca states, "..due to the wide range of blood collection times relative to dosing and the lack of a clear PK/PD relationship in the well-controlled exercise-challenge model in children (i.e., referring to Study No. 91688IL/0075) or in the chronic setting in adults, no attempt was made to correlate these concentrations with efficacy measures (i.e., referring to Study Nos. 9188IL/0079 anr 9188IL/0139)."

From HFD-570's reviewing medical officer it is noted that adverse events increase with dose but zafirlukast was originally thought to be a very safe drug. More recently cases of Churg-Strauss Syndrome or Eosinophillic Tissue Infiltration Syndrome are occurring plus many cases of hepatic enzyme elevations +/- symptoms. Noted also are two death-equivalent (one death and one liver transplant) cases because of hepatitis. [It is noted that zafirlukast is a drug that is extensively metabolized by the liver.]

3. **Is there PK data for the newly requested pediatric age range (i.e., to 11 years) and for the newly proposed dosing regimens (i.e., or 10 mg per day and 10 mg b.i.d. or 20 mg per day)?**

Answer: In this sNDA there is acceptable single dose (20 mg as 2 X 10 mg MT) and multiple dose (40 mg/per day as 2 X 10 mg MT b.i.d.) PK data for 20 healthy/mildly asthmatic children ages 7 to 11 years (Study No. 91881L/0145). From Study No. 9188IL/0058 there is single dose PK data (i.e., for doses of 2, 4, 6-8, 20-25, 30-40 and 50-70 mg) for cohorts of children, also 7 to 11 years and from Study No. 9188IL/0075 there are 4.5 hr post-dose drug concentrations (i.e., for relevant 5, 10 and 20 mg single doses) in children 6 to 14 years. However, there is no classical PK data for children years, or for the two newly proposed dosing regimens per se. In the absence of PK data for children years, only reasonable extrapolations of systemic drug exposure for the newly proposed dosing regimens

can be made for children 7 to 11 years who had PK data. (See review pages 11 to 12 for reported information/data).

4. **Are there differences in the PK characteristics of zafirlukast between boys and girls?**

Answer: From the OCPB review for the original NDA it states, "Pooled data where males and females were compared showed a higher unadjusted Cl/F for males. When Cl/F was adjusted for weight or lean body mass, apparent differences disappeared." For Study Nos. 9188IL/0145 and 9188IL/0058 boys and girls were enrolled. The findings from these two studies for the boy versus girl comparison similarly fall in line with what was observed in adult men and women as related to CL/F (i.e., unadjusted versus body weight adjusted). (See page 13 for summary results/comparisons)

5. **How do the PK characteristics of zafirlukast compare between children and adults, and what are the implications related to the newly proposed dosing regimens for zafirlukast for the younger children?**

Answer: When children (7 to 11 years) were studied using the currently approved adult dose/dosing regimen (Study No. 9188IL/0145), they had systemic drug exposure (i.e., Cmax and AUC) that was about twice that seen in adults (i.e., not hepatically impaired adults or elderly). An assessment of weight unadjusted oral clearance (CL/F) indicates that children in this age range have an average oral clearance that is about half that of adults. As a result, it is projected that systemic drug exposure in children (7 to 11 years) would be approximately the same as that for adults when using the newly proposed regimen of 10 mg b.i.d. Alternatively, the children's proposed starting regimen of [redacted] would result in lower systemic drug exposure which raises possible efficacy concerns. This, plus not having PK data in children [redacted] years to help assess dosing recommendations for this age range, raise concerns for supporting ACCOLATE's approval for children [redacted] years plus the [redacted] dosing regimen. Therefore, it is recommended to get more PK information/data to support ACCOLATE's use in children [redacted] years plus the lower proposed dose. (See review pages 14 to 15 for exposure and clearance information/comparisons).

[Note: In telecons held with Zeneca on 9/10/99 and 9/13/99, the company was informed that the NDA supplement would not be approved for i) children [redacted] years of age ii) the [redacted] dosing regimen and iii) the [redacted] tablet.]

Recommendation:

The Division of Pharmaceutical Evaluation II (DPEII) of the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed NDA 20-547 Supplement No. 007 that was submitted on 9/17/98 plus related subsequent submissions dated 2/11/99, 8/20/99, 8/26/99, 8/27/99, 9/3/99 and 9/10/99. DPEII/OCPB finds that the applicant has provided acceptable information and data to support the approval of the [redacted] and 10 mg tablet strengths. However, if there are clinical concerns regarding approval of the [redacted] dosing regimen, it may not be appropriate to approve the [redacted] tablet strength at this time. (See Synopsis; Answer to Question No. 5 above) Also, the applicant has provided acceptable and useful pharmacokinetic information and data for children 7 to 11 years using the adult zafirlukast dosing regimen. It is felt that this information can be used to help support ACCOLATE's approval for this age range and the 10 mg b.i.d. dosing regimen. However, due to the absence of pharmacokinetic

information/data for children [redacted] years, Comment No. 1 below should be communicated to the applicant. Comment Nos. 2 and 3 were previously communicated to the applicant and a response was received on 9/10/99 for Comment No. 3. Comment No. 4 should be forwarded to the applicant regarding the revised package insert submitted on 9/10/99.

1. It is requested that pharmacokinetic information/data be obtained in children [redacted] years of age in order to determine the correct dose for this age range. A protocol should be sent to the Agency for review and comment before the study is initiated.

2. The currently approved in vitro dissolution method for the 20 mg tablet is acceptable for the [redacted] and 10 mg tablets (i.e. [redacted] except that the acceptance specification should be changed to Q = [redacted] in [redacted] minutes for all three tablet strengths.

3. Currently, an attempt is being made to standardize the content and presentation of information that is to be given in the Clinical Pharmacokinetics section of the package insert. For this section there should be subheadings with appropriate information for Absorption, Distribution, Metabolism, and Excretion. Following this, there should be a section with the heading of Special Populations and appropriate subheadings (e.g., Geriatrics, Pediatrics, Hepatic Insufficiency, Renal Insufficiency, etc. as appropriate). Lastly, a table with mean (±SD) pharmacokinetic parameters for single dose and steady state conditions should be provided. Therefore, please modify your package insert as noted.

4. Regarding the revised package insert that was submitted on 9/10/99, the following should be addressed as related to the Clinical Pharmacokinetics, etc. sections.

   - Regarding the following statement, what is the source for the 45% value. From the table with the adult pharmacokinetic parameters that is now included in the package insert this value seems to be an overestimation based upon a comparison of Day 14 AUC(0-12) to Day 1 AUC(0-12).

     "Accumulation of zafirlukast in the plasma following twice daily dosing is approximately 45%."

   - For the table that has now been included with adult pharmacokinetic (PK) parameters, the reported values are from a study where [redacted] were administered. It would be better to provide PK parameters from a study that administered the approved 20 mg dose. Therefore, the PK parameters from Study No. 9188IL/0144 for the 10 mg to-be-marketed tablet for the 20 mg dose should replace the currently provided values.

   - For the subsection titled "Children" under **Special Populations**, it should be replaced with the following.

     "Children: Following a 20 mg dose of zafirlukast to 20 boys and girls between 7 and 11 years of age, a mean (%coefficient of variation) peak drug concentration of 601 ng/mL (45%) was obtained at about 2.5 hrs. Zafirlukast systemic exposure as determined by

mean AUC was 2027 ng.h/mL (38%). Weight unadjusted apparent oral clearance was 11.4 L/h (42%) which resulted in greater systemic drug exposure than that obtained in adults for an identical dose. Zafirlukast disposition was unchanged after multiple dosing (20 mg b.i.d.) in children and the degree of accumulation in plasma was similar to that observed in adults."

- Under the **Dosage and Administration** section, the subheading [redacted] should be changed to **Pediatric Patients 7 through 11 years of Age.** Additionally, the following changes should also be made for this subsection.

  1. The first sentence should be changed to read as, "The dosage in children 7 through 11 years of age is ACCOLATE 10 mg twice-daily."

  2. The second senteice should be deleted.

  3. The following sentence should be deleted due to the lack of bioavailability data to support administering the drug as noted.

[redacted]

/S/

John Hunt
Div. of Pharmaceutical Evaluation II

RD initialed by Mei-Ling Chen, Ph.D.
FT initialed by Mei-Ling Chen, Ph.D.

/S/
/S/
9/14/99

cc:
HFD-570 (NDA 20-547, Division File, Anthracite, Jani)
HFD-870 (M. Chen, Hunt, Uppoor)
HFD-340 (Viswanathan)
CDR (Barabara Murphy)

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Background:

For this sNDA, pediatric exclusivity does not apply because HFD-570 felt it needed data down to 6 months. When FDA's pediatric exclusivity letter was sent to Zeneca this supplement had already been submitted to FDA.

In addition to the Phase 1 type BA/PK studies noted in the Synopsis section above, the following two pivotal clinical safety and efficacy studies were conducted.

- Study No. 9188IL/0079: A randomized, double-blind, placebo-controlled, dose-ranging, parallel-group, multicenter safety and efficacy trial of zafirlukast (i.e., 5 or 10 mg b.i.d. for 4 weeks) in the treatment of pediatric subjects (5 to 11 years) with mild-to-moderate asthma. A total of 281 patients completed the trial. There was also an optional 52 week open label extension.

- Study No. 9188IL/0139: A randomized, double-blind, placebo-controlled, dose-ranging, parallel-group, multicenter safety and efficacy trial of zafirlukast (i.e., 10, 20 or 40 mg b.i.d. for 6 weeks) in the treatment of pediatric subjects (5 to 11 years) with mild-to-moderate asthma. A total of 379 patients completed the trial. There was an optional 52 week open label extension.

  Also conducted was Study No. 9188IL/0075 which was a randomized, multicenter, single-dose, double-blind, placebo-controlled trial in 2 parallel groups of pediatric patients (n = 18 per group; 6 to 14 years of age) with exercise-induced asthma. Each group had a balanced 3-period crossover design with a separation of 4 to 14 days between trial periods. During each treatment period, patients underwent exercise-challenge testing 4 hours after medication was given. In this study a single drug concentration was determined per subject per dose at about 4.5 hrs post-dose.

[Note: Although ACCOLATE is being marketed outside the U.S., it is not yet approved for use in children [redacted] year of age in foreign markets.]

Summary Pharmacokinetic (PK), Bioavailability (BA), etc. Information:

From the OCPB NDA review dated 6/20/96, some summary PK, BA, etc. information for zafirlukast is given below:

- Zarfirlukast plasma concentrations follow bi- or tri-exponential elimination PK.
- The mean terminal t1/2 was 9.3 hrs after a 20 mg oral solution dose (i.e., in 20% PEG 400) in healthy males.
- In a crossover fasting study (No. 9188US/0012; n = 12 normal healthy adult males, 19 to 35 yrs), 5, 10 and 20 mg tablet strengths (different formulation than MT) were proportional for AUC_{inf} (208, 425, and 868 ngxhr/mL, respectively) and Cmax (40.5, 92.4, and 210.9 ng/mL, respectively).
- Drug plasma protein binding, primarily to albumin, is >99%.
- The main route of elimination is via metabolism and excretion in feces (88.7%); urine accounts for 9.8% as metabolites.
- The 3 major metabolites found in plasma have 90 to 775 less fold potency at the leukotriene D_4 and E_4 receptors.
- In vitro studies indicated that zafirlukast may inhibit CYP3A4; two metabolites are formed by CYP2C9.

- Drug-drug interactions: aspirin increased zafirlukast AUC_{ss} about 45%; erythromycin and theophylline decreased zafirlukast AUCs about 34 and 22%, respectively; zafirlukast did not effect theopylline or ethinyl estradiol plasma concentrations.
- Two food effect studies demonstrated a 30 to 60% decrease in zafirlukast bioavailability.
- There is an indication of a possible circadian variation resulting in lower trough concentrations following AM dosing.
- There was no BE study (Phase III tablet vs. market tablet) for the 20 mg strength.

Review Questions:

Can the new and 10 mg tablet strengths be approved?

The new and 10 mg tablet strengths can be recommended for approval based on the following:

1. The new and 10 mg to-be-marketed tablets are compositionally proportional to the approved and marketed 20 mg tablet.

Table1: Ingredients of Market Tablets (mg/tablet).

Strength:	10 mg	20mg
Tablet Core:		
Zafirlukast	10.0	20.0
Croscarmellose Sodium, NF		
Lactose NF		
Microcrystalline Cellulose, NF		
Povidone, USP		
Magnesium Stearate, NF		
Tablet Coating:		
Hydroxypropyl – Methylcellulose USP		
Titanium Dioxide, USP		

Note: The site of manufacture for all tablet strengths is Carolina, Puerto Rico.

2. The and 10 mg MT tablets (production size batches) have similar in vitro dissolution profiles i) to each other, ii) to the and 10 mg tablets, respectively and iii) to the marketed 20 mg tablet (i.e., using the NDA approved dissolution method:

Table 2: Comparative In Vitro Dissolution Data.

	Tablet Strength (mg)	Batch No.	Type	Mean % Dissolution (%RSD) 15 min	30 min	45 min
A	20	4027S	MT[1]			
B	20	40201	MT[1]			
C	10	ST70125-016-FA01	PCT			
D	10	ST70125-016-FA04	PCT			
E	10	ST70125-016-FA03	PCT[2]			
F	10	40A1033	MT[1,2]			

The dissolution similarity factor (f_2) was determined for the comparisons of A vs B vs. F, C vs D vs. E vs. F, F vs The f_2 values were respectively. All comparisons indicate that the dissolution profiles are comparable (i.e., f_2)

3. There is acceptable in vivo single dose BE data for 2 X 10 mg MT vs. 2 X 10 mg PCT (Study No. 9188IL/0144; Table 3) and acceptable supportive multiple dose BE data for 1 X10 mg PCT b.i.d. vs. 2 X 5 mg PCT b.i.d. (Study No. 9188IL/0152; Table 4).

Table 3: Mean (%CV) PK parameters and 90% CI for 2 X 10 mg MT vs. 2 X 10 mg PCT (n = 36 adult males).

Treatment	Tmax (hr)	Cmax (ng/mL)	AUC_{inf} (ngxhr/mL)	MT/PCT Log Transformed 90%CI Cmax	AUC_{inf}
MT	2.1(47)	327(31)	1137(34)	0.89 – 1.05	0.92 – 1.00
PCT	2.0(44)	341(34)	1198(38)	PASS	PASS
Ratio		0.96	0.95		

Table 4: Mean (%CV) PK parameters and 90% CI for 1X 10 mg PCT vs. 2 X 5 mg PCT (n = 26 adult males).

Treatment	Tmax(hr)	Cmax (ng/mL)	AUC_{ss} (ngxhr/mL)	1X10 PCT/2X5 PCT Log Transformed 90% CI Cmax	AUC_{ss}
1X10 PCT	2.3(43)	154(34)	605(26)	0.80 – 0.97	0.85 – 0.96
2X5 PCT	2.2(40)	174(34)	675(31)	PASS	PASS
Ratio		0.89	0.90		

[Note: The 10 mg MT and 10 mg PCT formulations are identical except for the amounts of two tablet coating materials (i.e., hydroxypropyl methylcellulose: [redacted] per tablet, respectively; titanium dioxide: [redacted] per tablet, respectively). Also, the site of manufacture was different for the tested tablets. MT was made at the to-be-approved manufacturing site, Carolina, Puerto Rico, and PCT was made at Wilmington, Delaware. Lastly, the [redacted] and 10 mg PCT tablets contain the same formulation ingredients but the two tablet strengths are not exactly proportional like the [redacted] and 10 mg MT tablets.]

Is there PK data for the newly requested pediatric age range (i.e., [redacted] and for the newly proposed dosing regimens (i.e., [redacted] or 10 mg per day and 10 mg b.i.d. or 20 mg per day?

The available PK data for zafirlukast in children is summarized below in Tables 5 and 6.

1. Study No. 9188IL/0145

Table 5: Mean (%CV) PK parameters for healthy/mildly asthmatic children (n=20; 7-11 yrs).

Treatment	Tmax (hr)	Cmax(ng/mL)	C12 (ng/mL)	AUC_{0-12}	AUC_{inf}	Cl/F (L/h)	t1/2 (hr)
SD 2X10 mg MT (Day 1)	2.5(55)	601(45)	11.8(103)[1]	1944(38)[1]	2027(38)[2]	11.4(42)[2,3]	5.5(48)
MD, b.i.d. 2X10 mg MT (Day 15)	2.3(35)	644(43)	15.5(46)[1]	2300(42)	2476(42)	10.0(37)[4]	7.5(25)

[1] n = 19 [2] n = 18 [3] Using AUC_{inf} [4] Using AUC_{0-12}

2. Study No. 9188IL/0058

Table 6: Mean (%CV) single dose PK parameters for asthmatic children (7-11 yrs).

Dose (mg)	Tmax (hr)	Cmax (ng/mL)	AUC (ngxhr/mL)[1]	Cl/F(L/h)
2[2]	2.7(37)	33(45)	142(40)	16.2(39)
4[3]	3.0(37)	69(62)	370(32)	11.8(34)
6-8[2]	2.7(41)	81(37)	352(35)	18.9(19)
20-25[2]	3.3(30)	444(32)	1589(31)	14.1(35)
30-40[4]	2.4(58)	667(31)	2616(28)	12.7(28)
50-70[3]	2.7(37)	590(34)	2558(51)	23.1(41)

[1] AUC_{0-t} [2] n = 6 [3] n = 5 [4] n = 7

In addition to the summary PK parameters provided in Tables 5 and 6 above, the following findings are noted.

- From Study No. 9188IL/0145 which investigated the approved adult dosing regimen (i.e., 20 mg b.i.d.), to assess a possible change in PK as a function of repeated zafirlukast doses in children 7 to 11 years of age, last dose steady state AUC_{0-12} was compared to the first dose $AUC_{inf.}$ The obtained AUC ratio was 1.18 [90% CI (n = 18) for log-transformed AUC was 0.99 - 1.28]. Upon inspection of individual subject AUC ratios, half the subjects had ratios $\leq$ 1.0 and half had ratios >1.0. Overall, the results do not strongly suggest an apparent change in PK, at least over a time frame of about two weeks.

- From Study No. 9188IL/0145, an assessment of drug accumulation in children 7 to 11 years indicates that there is little but variable accumulation based upon comparisons of last day vs. first day Cmax, C12 and AUC_{0-12}. Accumulation ratios were 1.07, 1.31, and 1.18, respectively (90% CIs were 0.87-1.36, 1.19-2.02 and 1.03-1.18, respectively). Inspection of individual data for AUC indicated that 8 of 19 children had no accumulation and the remaining had some with a mean (range) accumulation ratio of 1.5 ( ) The sponsor states, "The greatest degree of accumulation in an individual (based on the ratio of AUC[0-12] – Day 15/1) was approximately 2.9. This degree of accumulation was within the range of accumulation that was found in trials that assessed zafirlukast in adults;".

- From Study No. 9188IL/0058, albeit with its sample size limitations per dose level, it suggests possible drug dose proportionality over the range of 2 to 20 mg. For Study No. 9188IL/0075, where a single 4.5 hr post-dose drug concentration was obtained for 5, 10, and 20 mg single zafirlukast doses (i.e., in asthmatic children 6 to 14 years), mean (CV) concentrations were 37.3 (40), 67.3 (47) and 104 (50), respectively, which also suggests possible drug dose proportionality. It is noted from Study No. 9188US/0012 that was previously reviewed by OCPB, dose proportionality was demonstrated for 5, 10 and 20 mg tablet strengths in adults.

Are there differences in the PK characteristics of zafirlukast between boys and girls?

From OCPB's review of the original NDA it indicates that males showed a higher unadjusted Cl/F than females. However, when Cl/F was adjusted for weight or lean body mass the apparent differences disappeared. In Study Nos. 9188IL/0145 and 9188IL/0058 both boys and girls were enrolled. Summarized below are the obtained apparent oral clearance values (i.e., unadjusted and adjusted for body weight) for boys and girls. The findings tend to fall in line with what was seen for adults.

Table 7: Mean apparent oral clearance values.

Study No.		CL/F (L/hr)			CL/F(L/hr/kg)		
		Boys	Girls	% Difference	Boys	Girls	% Difference
9188IL/0145[1]	n	8	10		8	10	
	Mean	12.4	10.6	17	0.358	0.336	7
	Median	11.8	7.8	51	0.315	0.298	6
9188IL/0145[2]	n	9	11		9	11	
	Mean	11.2	8.9	26	0.321	0.279	15
	Median	11.2	7.8	44	0.300	0.250	20
9188IL/0058[1,3]	n	18	17		18	17	
	Mean	17.2	15.1	14	0.512	0.508	1
	Median	16.1	13.7	18	0.442	0.434	2

[1] Single dose [2] Multiple dose [3] All studied dose levels

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How do the PK characteristics of zafirlukast compare between children and adults, and what are the implications related to the newly proposed dosing regimens for zafirlukast for the younger children?

Summarized in Table 8 are systemic exposure parameters (i.e., Cmax and AUC) plus apparent unadjusted oral clearance values that are from the studies submitted in this sNDA plus obtained from OCPB's previous NDA review.

Table 8: Comparative mean Cmax, AUC and unadjusted CL/F values.

Study No.	Dose(mg)	Subjects(N)	Cmax(ng/mL)	AUC_{inf}(ngxhr/mL)	Cl/F(L/hr)
9188US/0012	20[1]	Adults (12)	211	868	28.5
E-15-11	20[1]	Adults (6)	321	1183	21.1
9188IL/0062	20[1,2]	Adults (27)	233	980	20.4[3]
"	20[1,2]	Adults (27)	282	1067	18.7[3]
9188IL/0070	20[1,2]	Adults (23)	206	793	25.2[3]
"	20[1,2]	Adults (23)	212	817	24.5[3]
9188IL/0118	20[1]	Adults (11)	239	1025	22.8
9188IL/0144	20[1,2]	Adults (36)	327	1137	19.4
"	20[1,2]	Adults (36)	341	1198	16.7[3]
		Average of means:	264	1008	21.9
9188IL/0145	**20[1]**	**7 to 11 (20)**	**601**	**2027**	**11.4**
"	**20[4]**	**7 to 11 (20)**	**644**	**2300[5]**	**10.0**
9188US/0012	10[1]	Adults (12)	92	416	28.4
E-15-11	10[1]	Adults (6)	115	464	24.1
9188IL/0152	10[2,4]	Adults (26)	154	605[5]	17.8
"	10[2,4]	Adults (26)	174	676[5]	14.8[3]

[Note: The sponsor did CL/F analyses for adults vs. children that included a number of other adult studies that included doses other than those noted above as well as including studies that appear to not have been reviewed in the original OCPB review. The sponsor's analyses showed the mean (median) CL/F values to be 22.1 (20.7) L/hr and 14.0 (12.4) L/hr in adults and children, respectively. From Study No. 9188IL/0145 it is noted that 4 girls of different ages had low CL/F values between 5.5 and 6.9 L/hr and 1 had the highest determined value of 24.7 L/hr; boys clustered around the mean.]

[1] Single dose [2] One of 2 different treatments [3] Calculated from mean AUC [4] Dose in b.i.d. regimen
[5] Steady state $AUC_{0\text{-}12}$

From the data presented in Table 8 the following is noted.

- Following a 20 mg oral dose of zafirlukast in children 7 to 11 years of age, Cmax is 2 fold greater than that seen in adults for the same dose. Likewise, AUC is also about two fold greater on average in children than adults.

- The difference seen in systemic exposure between the children and adults is due to the fact that the apparent oral clearance in children is about half that seen in adults.

Has an acceptable drug assay procedure been used for the BE/PK studies?

For Study Nos. 9188IL/0144, 9188IL/0145 and 9188IL/0152 they used the same assay method (i.e., [redacted] that was used for a number of studies reviewed in the original NDA including pivotal BE studies and Study No. 9188IL/0058. The assay covered a range of [redacted] Collected samples with high drug concentrations were diluted appropriately. Assay quality control data for the three studies is summarized below.

Table 9: Assay performance.

Study No.	Quality-control concentration (ng/mL)	Accuracy (% of theory)	Precision (SD/mean)x100
9188IL/0144	2.0	101	7.3
	40.0	96.9	5.9
	100	97.9	4.2
9188IL/0145	2.0	98.4	5.8
	40.0	101	3.4
	100	104	3.6
9188IL/0152	2.0	101	4.6
	40.0	107	4.5
	100	104	4.3

The assay is considered acceptable for the reviewed studies.

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Appendix

Study Protocol Summaries

Study No. 9188IL/0144

Title: A Trial Comparing the Bioavailability of Single 20 mg Doses of Pediatric Sales Tablets and the Pediatric Clinical Trial Tablets of Zafirlukast (ACCOLATE)

NDA Location: Volume 7.8

Investigator:

Objective:

The primary objective was to compare the bioavailability of zafirlukast administered as a single 20 mg (2 x 10mg) dose of the sales tablet and a single20 mg (2 x 10 mg) dose of the clinical trial tablet. The secondary objective is to determine the safety of single 20 mg doses of the pediatric zafirlukast tablet.

Dosage Forms:

10 mg Sales Tablet (Formula Batch No. 40A1033)
10 mg Clinical Trial Tablet (Formula Batch No. ST70125-016-FA03)

Study Design:

This was a double-blind, randomized 2 period crossover study. Thirty-seven healthy, adult males were enrolled but subject dropped out because of a family emergency. Inclusion criteria were that the men had to be between 18 to 50 years of age and weigh between 110 to 220 lbs. Also, there was to be no smoking history within 6 months of screening. The subjects resided at the clinical center from Day 1 through the morning of Day 8. Drug treatments were given on Days 2 and 6. Subjects fasted for 8 hrs before and 4 hrs post-drug administration. Each study treatment was given with 250 mL of room-temperature water. Blood samples (5 mL) were collected prior to drug administration and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42, and 48 hrs. post-dose. Plasma was harvested and samples were assayed at the Drug Disposition and Metabolism Department of Zeneca.

Results: See review page 10, Table 3.

Conclusions:

The study is acceptable and it demonstrates the two studied 10 mg tablet formulations to be bioequivalent.

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Study No. 9188IL/0145

Title: A Trial to Evaluate the Pharmacokinetics, Safety, and Tolerability of Single and Multiple Doses of a New Pediatric Sales Formulation of Zafirlukast (ICI 204,219, ACCOLATE) in Healthy to Mildly Asthmatic Pediatric Population

NDA Location: Volume 7.7

Investigator:

Objective:

The primary objective is to determine the pharmacokinetics, safety, and tolerability of a 20 mg dose of a new sales formulation of zafirlukast (2 x 10 mg 6 mm tablets) adiministered as a single dose and as multiple doses to pediatric subjects aged 5 through 11 years. Secondary objectives are to define the safety and tolerability of zafirlukast in this pediatric population.

Dosage Form:

10 mg Sales Tablet (Formula Batch No. 40A1033)
Placebo Tablet (Formula Batch No. ST70255-027-FA01)

Study Design:

This was an open-label, 2 period, single center, single and multiple dose, 16 day trail. Twenty healthy or mildly asthmatic pediatric subjects were enrolled. Inclusion criteria were that the subjects were to be 5 to 11 years of age, and weigh between 35 to 120 lbs. Subjects were not to require the use of oral corticosteroids. Except for inhaled cromolyn sodium, inhaled corticosteroids, inhaled beta-agonist or trial medication, no other medications were to be allowed. Subjects came to the clinical research center (CRC) on Day 1 having fasted for at least 8 hrs. The first dose was taken with 30 to 120 mL of room-temperature water. Subjects continued fasting for 4 hrs. post-dose. On Day 2 the second dose was given and for Days 2 through 14 drug was administered every 12 hrs. on an outpatient basis. On the morning of Day 15 the subjects returned to the CRC having fasted for 8 hrs. to get the final dose at the appropriate 12 hr. interval. Blood samples (3 mL) were collected on Days 1 and 15 pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hrs. post-dose. Plasma was harvested and samples were assayed at the Drug Disposition and Metabolism Department of Zeneca.

Results: See review page 11, Table 5.

Conclusions:

The study is acceptable in providing PK data using the adult approved dose/dosing regimen. It is noted that although children 5 to 11 years of age were to be enrolled, only children 7 to 11 were studied.

Study No. 8188IL/0152

Title: Evaluation of the Dose-proportionality of 2 Different Zafirlukast (ICI 204,219, ACCOLATE) Tablets in Healthy Adult Subjects

NDA Location: Volume 7.9

Investigator: [redacted]

Objectives:

The primary objective of this trial is to evaluate the dose-proportionality of two 5 mg tablets of zafirlukast compared with a single 10 mg tablet.

Dosage Forms:

5 mg Clinical Trial Tablet (Formula [redacted] Batch No. ST70124-012-FA03)
10 mg " " " (Formula [redacted] Batch No. ST70125-016-FA04)

Study Design:

This was a randomized, single center, open label, 2 period, crossover, multiple dose trial. Twenty eight healthy men were enrolled and 26 completed the trial. Inclusion criteria indicated that subjects should be between the ages of 10 to 50 years and weight within 20 % of ideal body weight. Also, there was to be no smoking history within 6 months of the start of the trial. The trial consisted of two 6 day treatment periods. Subjects were given one 10 mg tablet or two 5 mg tablets during Period 1 every 12 hrs. After at least a two day washout they were given the alternative treatment. During the trial, meals were to be consumed at least 3 hrs. before each dose or at least 2 hrs. after each dose. On the morning of PK sampling subjects were fasted 4 hrs. post-dose. Blood samples (7 mL) were collected on the morning of Day 6 pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hrs post-dose. Plasma was harvested and samples were assayed at the Drug Disposition Department of Zeneca.

Results: See review page 11, Table 4.

Conclusions:

The study is acceptable and it demonstrates that 2 X 5 mg pediatric clinical trial tablet is bioequivalent to 1 X 10 mg pediatric clinical trial tablet under multiple dosing conditions (i.e., b.i.d.). It is noted that is not technically a dose-proportionality study as indicated by the sponsor because only one dose is given (i.e., 20 mg b.i.d.).

22. SAFETY AND PHARMACOKINETICS OF SINGLE ORAL DOSES OF ICI 204,219 IN CHILDREN WITH ASTHMA (9188IL/0058)

Reference: IND [redacted] Sec. 278, Vol.60.25, p.1
Investigators:
Clinical facility: [redacted]

Objectives

To determine the safety and pharmacokinetics of single oral doses of zafirlukast (ICI 204,219) in children with asthma.

Drug Dosage Form

The following tablets of ICI 204,219 (zafirlukast) were used in this study:

2 mg tablets of ERB formulation	Lot # ST70274-001-FA03
5 mg tablets of ERB formulation	Lot # ST70124-006-FA03
10 mg tablets of ERB formulation	Lot # ST70125-014-FB04
20 mg tablets of ERB formulation	Lot # ST70126-014-FA04
40 mg tablets of ERB formulation	Lot # ST70199-002-FA02
placebo [redacted]	Lot # ST70255-001-FA04

Subjects

Eighteen black asthma patients (9 boys, 9 girls) participated in the study. The ages ranged from 7 to 11 years (mean 9) and the weights ranged from 22.6 to 54.3 kg (mean 32.8).

Study Design

This study was a double-blind, randomized, two-period crossover trial. Subjects remained in the clinical facility from the afternoon of Day 1 to the morning of Day 3 (returned briefly in late afternoon of Day 3) for each of the two trial periods. Drug administration occurred on Day 2. Periods were separated by 7 to 14 days. Subjects were divided into three groups (I, II and III). Group I received 0.05 and 0.5 mg/kg, Group II received 0.1 and 1.0 mg/kg and Group III received 0.2 mg/kg and 1.6 mg/kg (not to exceed 80 mg). Subjects fasted for 8 hours before and 4 hours after dosing. Blood samples were collected at 0, 0.5, 1, 2, 4, 6, 9, 12, 16, 20, 24 and 32 hours after dosing.

Analytical Methodology

Investigator & Site: [redacted]

According to the study report, plasma samples were analyzed using method [redacted] The lower limit of quantitation was [redacted] and the upper limit was [redacted] (greater with dilution of samples). The imprecision for the assay during the processing of these samples (%RSD based on assay of control samples) ranged from [redacted]

Results

The mean (%CV) plasma zafirlukast pharmacokinetic parameters are:

Group	I	II	III	I	II	III
Dose, mg/kg	0.05	0.14	0.22	0.52	1.11	1.69
C_{max}, ng/ml	33 (45)	69 (60)	81 (36)	444 (32)	667 (32)	590 (34)
t_{max}, h*	2.1 (2, 4)	3.0 (2, 4)	2.0 (2, 4)	4.0 (2, 4)	2.1 (1, 4)	2.1 (2, 4)
$t_{1/2}$, h	NC	NC	NC	11.5 (39)	8.7 (28)	9.3 (24)
$AUC_{0-\infty}$ ng•h/ml	142 (40)	312 (57)	352 (36)	1589 (31)	2717 (27)	2438 (49)
$AUC_{0-\infty}$, ng•h/ml	NC	NC	NC	1621 (34)	2740 (27)	2205 (50)
Cl/F, L/h/kg	0.39 (28)	0.43 (31)	0.67 (30)	0.34 (22)	0.42 (20)	0.80 (41)
V/F, L/kg	NC	NC	NC	6 (37)	5 (49)	13 (52)

* median (range)
NC = not calculated

C_{max} and AUC values increased proportionally with dose. The weight-normalized Cl/F was not significantly different between groups or between doses in the age range of the study (7-11 years) and did not vary with age.

Comments

For the calculation of pharmacokinetic parameters, some not quantifiable concentrations [redacted] occurring at the beginning or end of the quantifiable samples, were treated as [redacted] while other similar cases were not. These values should all be treated as 0.

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